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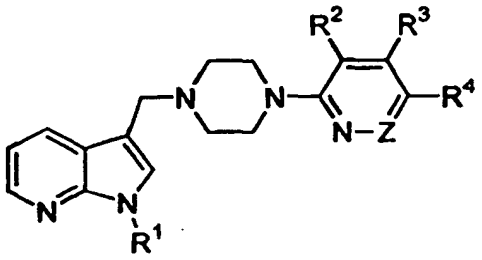
(54) Title: DOPAMINE D4 RECEPTOR LIGANDS

(57) Abstract

Described herein are D4 receptor–selective compounds of formula (I) wherein Z is selected from N and C(R^5); R^1 is selected from H and an acid labile protecting group; R^2, R^3, R^4 and R^5 are independently selected from H, hydroxy, loweralkyl, loweralkyl optionally substituted with one or more groups selected from halo, hydroxy and loweralkoxy; loweralkyl–S–, halo, radioisotopic halo, loweralkoxy, trifluoromethylsulfonyl, cycloalkyl, aryl and tri(loweralkyl)tin; with the proviso that when Z is C(R^5) then at least one of R^2, R^3, R^4 and R^5 are selected from radioisotopic halo and tri(loweralkyl)tin; and salts, solvates or hydrates thereof. Also described is the use of these compounds as pharmaceuticals to treat indications for which a dopamine D4 receptor antagonist is indicated. Radiolabeled compounds are useful particularly to image localization of D4 receptor in the human brain, and can therefore aid in the diagnosis of schizophrenia and other medial conditions in which the D4 receptor is implicated.



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DOPAMINE D4 RECEPTOR LIGANDS

This invention relates to compounds that bind to the dopamine D4 receptor, and to their use for therapeutic and diagnostic purposes.

Background to the Invention

Neuronal cell receptors that bind the neurotransmitter dopamine constitute a group of at least five structurally distinct proteins that can now be produced using recombinant DNA techniques. These techniques have been applied to construct cell lines that incorporate the dopamine receptor in their membranes, to provide regenerable and homogeneous substrates with which chemical libraries can be screened to identify potential CNS-active drugs.

Recent evidence strongly implicates the dopamine receptor classified as D4 in the etiology of schizophrenia. It has been suggested that compounds capable of interfering with the function of this receptor, which is present in schizophrenics at levels that are six times normal, would be useful in the treatment of this disease (Seeman et al, Nature, 1993, 365:441). Some dopamine receptor ligands currently sold as pharmaceuticals exhibit the desired affinity and antagonism for the D4 receptor, yet interact non-selectively with related dopamine receptors, particularly the D2 receptor type, which results in significant side effects that include altered motor function and tachycardia. It would be desirable to provide compounds that exhibit not only a high degree of affinity for the D4 receptor, but also a relatively low degree of affinity for the D2 receptor. In this specification, this desired combination of receptor binding properties is referred to as D4 selectivity.

Products currently marketed to treat indications in which the D4 receptor function is implicated include the dibenzodiazepine, clozapine, and the dibenzoxazepine, isoloxapine. Analysis of their dopamine receptor binding properties

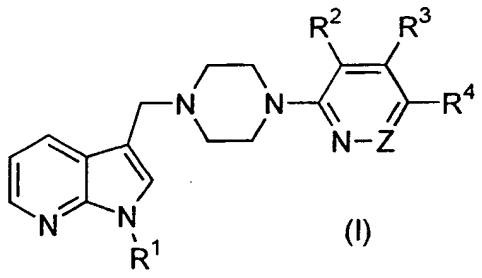
has shown that the preference for binding to the D4 receptor relative to the D2 receptor is about 10 fold, for both products. Similarly, both bind to the D4 receptor with about the same affinity (Ki value approximately 20 nM).

Recently, other D4 receptor antagonists have been identified (see, for example, Baker et al. US patent 5,576,336 issued November 19, 1996; Baker et al. US patent 5,622,950 issued April 22, 1997; and Baker et al. US patent 5,432,177 issued July 11, 1995; and Pollak et al. US patent 5,725,838 issued March 10, 1998). Although these compounds are more selective for the D4 receptor than previous compounds, they still exhibit significant binding at other receptors found within the brain. It would therefore be desirable to provide compounds that are more selective for the D4 receptor in the development of therapeutic agents.

In the context of medical diagnostics, this non-selective binding at the D4 receptor prevents the generation of an accurate image of the localization and prevalence specifically of the D4 type of dopamine receptor. It would therefore be desirable to provide compounds that, in their radiolabeled state, bind at the D4 receptor with affinity and selectivity appropriate for diagnostic imaging purposes. When used in combination with such diagnostic imaging techniques as single photon emission tomography (SPECT) and positron emission tomography (PET), such radiolabeled compounds would be useful particularly to diagnose schizophrenia and other medical conditions associated with D4 receptor anomalies.

Summary of the Invention

According to one aspect of the present invention, there are provided compounds of Formula (I):



(I)

wherein Z is selected from N and C(R^5); R^1 is selected from H and an acid labile protecting group; R^2, R^3, R^4 and R^5 are independently selected from H, hydroxy, loweralkyl, loweralkyl optionally substituted with one or more groups selected from halo, hydroxy and loweralkoxy; loweralkyl-S-, halo, radioisotopic halo, loweralkoxy, trifluoromethylsulfonyl, cycloalkyl, aryl and tri(loweralkyl)tin; with the proviso that when Z is C(R^5) then at least one of R^2, R^3, R^4 and R^5 are selected from radioisotopic halo and tri(loweralkyl)tin; and salts, solvates or hydrates thereof.

According to another aspect of the invention, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Formula (I) wherein Z is N, R^1 is as defined hereinabove, and R^2, R^3 and R^4 are independently selected from H, hydroxy, loweralkyl, loweralkyl optionally substituted with one or more groups selected from halo, hydroxy and loweralkoxy; loweralkyl-S-, halo, loweralkoxy, trifluoromethylsulfonyl, cycloalkyl and aryl, in an amount effective to antagonize D4 receptor stimulation.

In still another of its aspects, the invention provides the use of compounds of Formula (I) wherein Z is N and R^1, R^2, R^3 and R^4 are as defined hereinabove, as D4

receptor antagonists for the treatment of medical conditions mediated by D4 receptor stimulation.

According to another aspect of the invention, there is provided a radiopharmaceutical composition comprising a pharmaceutically acceptable carrier such as physiological buffered saline and a compound of Formula (I) wherein at least one of R^2, R^3, R^4 and R^5 is a radioisotopic halo.

In a further aspect of the invention, there is provided a method for imaging D4 receptors *in vivo*, comprising the step of administering systemically to a patient an effective amount of a radiopharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Formula (I) wherein at least one of R^2, R^3, R^4 and R^5 is a radioisotopic halo, allowing the radiopharmaceutical to localize within the brain, and then taking an image of the brain of the patient so treated.

Detailed Description of the Invention

The term 'loweralkyl' as used herein means straight chain alkyl radicals containing from one to six carbon atoms and branched chain alkyl radicals containing three to six carbon atoms and includes methyl, *n*-butyl, 1-methylethyl and the like.

The term 'alkoxycarbonyl' as used herein means straight and branched chain alkyl carbonates containing from two to six carbon atoms and includes methoxycarbonyl, ethoxycarbonyl, *t*-butoxycarbonyl and the like.

The term 'halo' as used herein means a halogen radical selected from bromo, chloro, iodo or fluoro. Radioisotopic halo include ^{123}I, ^{124}I, ^{125}I, ^{131}I, ^{18}F, and ^{76}Br.

The term 'cycloalkyl' as used herein means saturated or unsaturated non-aromatic cyclic hydrocarbon containing from 3 to 6 carbon atoms, and includes cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term acid labile protecting group as used herein means a protecting group that affords protection to the functional group to which it is attached from undesired side reactions yet is cleavable from the molecule under acidic conditions. In this particular case the protecting group serves to stabilize the trialkyltin molecule to enable it to be isolated. During the course of the radioiodination reaction, after the initial iodine for tin exchange, the acidic conditions of the reaction cause the protecting group to be removed hence giving the final deprotected and radiolabelled molecule. Suitable acid labile protecting groups are disclosed in, for example, T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2nd Edition, 1991, John Wiley & Sons Inc., New York, and include groups such as *t*-butoxycarbonyl.

Compounds of the present invention are those of Formula (I) in which R^1, R^2, R^3, R^4 and R^5 are as defined above.

A preferred group of compounds of this invention are represented by Formula (I) wherein Z is N, R^1 is selected from H, alkoxycarbonyl and alkoxyalkyl, and R^2, R^3 and R^4 are independently selected from H, halo, radioisotopic halo, loweralkyl, loweralkoxy, hydroxy, phenyl, trifluoromethylsulfonyl, tributyltin and trimethyltin.

A more preferred group of compounds of this invention is represented by Formula (I) wherein Z is N, R^1 is selected from H, *t*-butoxycarbonyl and methoxymethyl, and R^2, R^3 and R^4 are independently selected from H, I, Cl, Br, F, ^{123}I, ^{124}I, ^{125}I, ^{131}I, ^{18}F, ^{76}Br, phenyl, tributyltin, trimethyltin and methoxy.

A most preferred group of compounds of this invention are represented by Formula (I) wherein Z is N, R^1 is selected from H and *t*-butoxycarbonyl, and R^2, R^3 and R^4 are independently selected from H, I, Cl, ^{123}I, phenyl, trimethyltin and methoxy.

Another preferred group of compounds of this invention are represented by Formula (I) wherein Z is $C(R^5)$, R^1 is selected from H, alkoxycarbonyl and alkoxyalkyl,

and R^2, R^3, R^4 and R^5 are independently selected from H, halo, radioisotopic halo, loweralkoxy, tributyltin and trimethyltin with the proviso that at least one of R^2, R^3, R^4 and R^5 are selected from radioisotopic halo, tributyltin and trimethyltin.

A more preferred group of compounds of this invention is represented by Formula (I) wherein Z is $C(R^5)$, R^1 is selected from H, *t*-butoxycarbonyl and methoxymethyl, and R^2, R^3, R^4 and R^5 are independently selected from H, ^{123}I, ^{124}I, ^{125}I, ^{131}I, ^{18}F, methoxy, tributyltin, trimethyltin and methoxy with the proviso that at least one of R^2, R^3, R^4 and R^5 are selected from ^{123}I, ^{124}I, ^{125}I, ^{131}I, ^{18}F, tributyltin and trimethyltin.

A most preferred group of compounds of this invention are represented by Formula (I) wherein Z is $C(R^5)$, R^1 is selected from H and *t*-butoxycarbonyl, and R^2, R^3, R^4 and R^5 are independently selected from H, ^{123}I, methoxy and trimethyltin with the proviso that at least one of R^2, R^3, R^4 and R^5 are selected from ^{123}I and trimethyltin.

Acid addition salts of the compound of Formula (I) are most suitably formed from pharmaceutically acceptable acids, and include for example those formed with inorganic acids e.g. hydrochloric, sulphuric or phosphoric acids and organic acids e.g. succinic, maleic, acetic or fumaric acid. Other non-pharmaceutically acceptable salts e.g. oxalates may be used for example in the isolation of compounds of Formula I for laboratory use, or for subsequent conversion to a pharmaceutically acceptable acid addition salt. Also included within the scope of the invention are solvates and hydrates of the invention.

The conversion of a given compound salt to a desired compound salt is achieved by applying standard techniques, in which an aqueous solution of the given salt is treated with a solution of base e.g. sodium carbonate or potassium hydroxide, to liberate the free base which is then extracted into an appropriate solvent, such as ether. The free base is then separated from the aqueous portion, dried, and treated with the requisite acid to give the desired salt.

Compounds of Formula (I) containing radioactive isotopes, for example ^{123}I, ^{124}I, ^{125}I, ^{18}F for use as radiopharmaceuticals are typically prepared by either nucleophilic displacement of a suitable leaving group (for example trifluoromethylsulfonate) using for example potassium ^{18}F fluoride by methods known to one skilled in the art, or by an electrophilic substitution of a suitable group (for example trialkyltin) using for example sodium ^{123}I iodide in the presence of a suitable oxidant (for example chloramine-T), or related methods known to one skilled in the art (Hasrat, A. and Van Lier, J. *Synthesis*, 1996, 425).

Compounds of Formula (I) wherein R^1 is H and one or more of R^2, R^3, R^4 and R^5 is a radioisotopic iodide, can be prepared by reacting a compound of Formula (I) wherein one or more of R^2, R^3, R^4 and R^5 is tri(loweralkyl)tin and R^1 is H or an acid labile protecting group, with radioisotopic iodide source, for example a solution of radioisotopic sodium iodide (e.g. as a solution in 1N NaOH), in the presence of an acid and an oxidizing agent in an alcoholic solvent. Preferred conditions are Chloramine T and hydrochloric acid in ethanol.

In a preferred method, compounds of Formula (I) wherein R^1 is H and one or more of R^2, R^3, R^4 and R^5 is a radioisotopic iodide, are prepared by reacting a compound of Formula (I) wherein one or more of R^2, R^3, R^4 and R^5 is tri(loweralkyl)tin and R^1 is alkoxycarbonyl, with a radioisotopic iodide source as described above, followed by removal of the alkoxycarbonyl protecting group under acidic conditions in the same reaction vessel. The preferred acid is hydrochloric acid.

To generate compounds of the Formula (I) wherein Z is $C(R^5)$, R^1 is H and R^2, R^3, R^4 and R^5 are as described hereinabove, an appropriately substituted piperazine is coupled with 1H-pyrrolo[2,3-b]pyridine in the presence of formaldehyde in an aqueous buffer solution, for example aqueous sodium acetate in acetic acid. The 1H-pyrrolo[2,3-b]pyridine is commercially available and the piperazines are either commercially available or can be prepared by methods known to one skilled in the art. Thus 1-(pyridin-2-yl)piperazine is coupled with 1H-pyrrolo[2,3-b]pyridine in the

presence of formaldehyde in a buffer made up of sodium acetate and acetic acid. The substituted piperazines are prepared by reaction of an appropriately substituted pyridine with piperazine in the presence of a base in an inert solvent such as acetonitrile, at temperatures between 0 and 100°C, preferably at reflux. Suitable bases include piperazine itself, sodium or potassium carbonate.

Compounds of the Formula (I) wherein Z is $C(R^5)$, R^1 is H and R^2, R^3, R^4 and R^5 are as described hereinabove can also be prepared by treatment of an appropriately substituted piperazine with 3-(N,N-dimethylaminomethyl)-1H-pyrrolo[2,3-b]pyridine in a suitable inert solvent, preferably toluene, at a temperature between 50-120°C preferably at reflux. Thus 1-(5-iodopyridin-2-yl)piperazine is coupled with 1H-pyrrolo[2,3-b]pyridine in toluene at reflux.

To generate compounds of the Formula (I) wherein Z is N, R^1 is H and R^2, R^3, and R^4 are as described hereinabove, an appropriately substituted piperazine is coupled with 1H-pyrrolo-[2,3-b]-pyridine in the presence of formaldehyde in an aqueous buffer solution, for example aqueous sodium acetate in acetic acid. The 1H-pyrrolo-[2,3-b]-pyridine is commercially available and the piperazines are either commercially available or can be prepared by methods known to one skilled in the art. Thus 1-[6-iodopyridazin-3-yl)piperazine is coupled with 1H-pyrrolo-[2,3-b]-pyridine in the presence of formaldehyde in a buffer made up of sodium acetate and acetic acid. The 1-[6-iodopyridazin-3-yl)piperazine can be prepared from 3,6-diiodopyridazine by reaction with piperazine in a suitable solvent, for example acetonitrile, at reflux. The 3,6-diiodopyridazine is prepared as described in the literature (P. Coad et al. Journal of Organic Chemistry, 1963, 28, 218)

Compounds of the Formula (I) wherein Z is N, R^1 is H and R^2, R^3 and R^4 are as described hereinabove can also be prepared by treatment of an appropriately substituted piperazine with 3-(N,N-dimethylaminomethyl)-1H-pyrrolo-[2,3-b]-pyridine in a suitable inert solvent preferably toluene at a temperature between 50-120°C

preferably at reflux. Thus 1-[6-iodopyridazin-3-yl)piperazine is coupled with 1H-pyrrolo-[2,3-b]-pyridine in toluene at reflux.

Compounds of Formula (I) wherein R^1 is alkoxycarbonyl and Z, R^2, R^3, R^4 and R^5 are as described hereinabove can be prepared by reacting compounds of Formula (I) wherein R^1 is H and Z, R^2, R^3, R^4 and R^5 are as described hereinabove with dialkoxydicarbonate reagents in the presence of a base in an inert solvent at temperatures in the range of 0-50°C, preferably at around room temperature. Suitable bases include sodium or potassium hydroxide or triethylamine. Suitable inert solvents include chloroform, dichloromethane or acetonitrile. Preferred conditions are potassium hydroxide in dichloromethane. The dialkoxydicarbonate reagents are readily available protecting group reagents.

Compounds of Formula (I) wherein R^1 is alkoxycarbonyl and one or more of R^2, R^3, R^4 and R^5 are tri(loweralkyl)tin can also be prepared by reacting compounds of Formula (I) wherein R^1 is alkoxycarbonyl and one or more of R^2, R^3, R^4 and R^5 is iodo with hexa(loweralkyl)ditin reagents under standard palladium catalyzed cross-coupling conditions, for example, in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium (0) in an inert solvent, for example, toluene at temperatures ranging from 50-120°C preferably at about 110°C.

In a preferred embodiment of the invention, the compounds are selected from:

3-[4-(6-chloropyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(pyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(6-methoxy-5-trimethylstannylpyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(6-methoxy-5-iodopyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(6-methoxypyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo-[2,3-b]pyridine;
3-[4-(6-iodopyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

1-*t*-butoxycarbonyl-3-[4-(6-iodopyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

1-*t*-butoxycarbonyl-3-[4-(6-trimethylstannylpyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

^{123}I-3-[4-(6-iodopyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

3-[4-(6-methylpyridazin-3-yl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

3-[4-(6-iodo-5-methylpyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

3-[4-(6-hydroxypyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

3-[4-(6-trifluoromethanesulfonyloxypyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

3-[4-(6-phenylpyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

3-[4-(3,5-dichloropyridin-2-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

^{123}I-3-[4-(5-iodopyridin-2-yl)-piperazin-1-yl]methylpyrrolo[2,3-b]pyridine; and

1-t-butoxycarbonyl-3-[4-(5-trimethylstannylpyridin-2-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine.

In a more preferred embodiment of the invention, the compounds are selected from:

3-[4-(6-chloropyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

3-[4-(pyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

3-[4-(6-methoxypyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo-[2,3-b]pyridine;

3-[4-(6-iodopyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

1-*t*-butoxycarbonyl-3-[4-(6-iodopyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

1-*t*-butoxycarbonyl-3-[4-(6-trimethylstannylpyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

^{123}I-3-[4-(6-iodopyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

3-[4-(6-methylpyridazin-3-yl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

3-[4-(6-phenylpyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

^{123}I-3-[4-(5-iodopyridin-2-yl)-piperazin-1-yl]methylpyrrolo[2,3-b]pyridine; and

1-t-butoxycarbonyl-3-[4-(5-trimethylstannylpyridin-2-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine.

The compounds of the invention wherein one or more of R^2, R^3, R^4 and R^5 are radioisotopic iodide are formulated as radiopharmaceutical compositions together with any physiologically and radiologically tolerable vehicle appropriate for administering the compound systemically. Included among such vehicles are phosphate buffered saline solutions, buffered for example to pH 7.4.

For use in medicine, the compounds of the present invention can be administered in a standard pharmaceutical composition. The present invention therefore provides, in a further aspect, pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a Formula (I) compound or a pharmaceutically acceptable salt, solvate or hydrate thereof, in an amount effective to antagonize D4 receptor stimulation.

The compounds of the present invention may be administered by any convenient route, for example by oral, parenteral, buccal, sublingual, nasal, rectal or transdermal administration and the pharmaceutical compositions formulated accordingly.

Compounds of Formula (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as liquids, for example syrups, suspensions or emulsions, or as solid forms such as tablets, capsules and lozenges. A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable pharmaceutical liquid carrier for example, ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavouring or colouring agent. A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose. A composition in

the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier, for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilized and then reconstituted with a suitable solvent just prior to administration.

Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device. Alternatively, the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal after use. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas such as compressed air or an organic propellant such as fluorochlorohydrocarbon. The aerosol dosage forms can also take the form of a pump-atomizer.

Compositions suitable for buccal or sublingual administration include tablets, lozenges, and pastilles, wherein the active ingredient is formulated with a carrier such as sugar, acacia, tragacanth, or gelatin and glycerine. Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base such as cocoa butter.

Preferably, the composition is in unit dose form such as a tablet, capsule or ampoule. Suitable unit doses i.e. therapeutically effective amounts; can be determined during clinical trials designed appropriately for each of the conditions for which administration of a chosen compound is indicated and will of course vary depending on the desired clinical endpoint. It is anticipated that dosage sizes appropriate for administering the compounds of the examples will be roughly equivalent to, or slightly less than, those used currently for clozapine. Accordingly, each dosage unit for oral administration may contain from 1 to about 500 mgs, and will be administered in a frequency appropriate for initial and maintenance treatments.

For imaging and diagnostic purposes, it is contemplated that the present compounds will be administered to patients by intravenous injection or infusion at doses suitable (e.g. between 1 and 10 mCi) to generate an image of the compound as localized within the brain, using for example a gamma camera. Preferably, the compounds will be administered and allowed to localize within the brain for 30 minutes to 48 hours prior to generating an image of the brain of the patient so treated. It is further contemplated that the method of the present invention can usefully be applied diagnose to patients suspected of suffering from schizophrenia. For these patients, diagnosis can be aided or confirmed by determining the intensity of radiolabeled compound relative to the brain of a healthy patient; greater image intensity is indicative of an overabundance of D4 receptor, and is hence indicative of a schizophrenic condition.

Example 1: Preparation of 3-[4-(6-chloropyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine

A mixture of 3-chloro-6-(1-piperazinyl)-pyridazine (100 mg, 0.425 mmol) and sodium acetate (58 mg, 0.425 mmol), in water (0.5 mL) and acetic acid (1.0 mL) was added 37% formaldehyde (33 OL, 0.468 mmol). After 10 minutes stirring, 7-azaindole (50.3 mg, 0.425 mol) was added. The reaction was stirred for 24 h.

Strong ammonium hydroxide (1 mL) was added and the product extracted into dichloromethane (3 mL). The solvent was concentrated to a white solid. The product was purified by chromatography on a flash silica gel column using dichloromethane:methanol:ammonia (50:7:1) to give the title compound as a white solid (65 mg, 47% yield). δH (DMSO-d_6) 2.60 (4H, m, piperazinyl CH_2); 3.62 (4H, m, piperazinyl CH_2); 3.75 (2H, s, CH_2); 7.06 (1H, t); 7.35 (1H, d, J =9.6); 7.40 (1H, s); 7.51 (1H, d, J= 9.6); 8.07 (1H, d, J = 7.8); 8.22 (1H, d); 11.48 (1H, br s, NH): ESMS 329 (M^+ +1).

Example 2: Preparation of 1-*t*-butoxycarbonyl-3-[4-(6-iodopyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine

To a solution of 3-[4-(6-iodopyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine (110 mg, 0.26 mmol) and KOH (44 mg, 0.7 mmol) in dichloromethane (2 mL) at room temperature was added di-tert-butyldicarbonate (63 mg, 0.28 mmol). The mixture was stirred at room temperature for 3 h and was then filtered. The residue was washed with dichloromethane and the solvents removed under reduced pressure. The resulting residue was purified by column chromatography on silica gel using ethyl acetate: dichloromethane 7:3 as eluent to give the title compound as a colourless foam (133 mg, 98 % yield). δH ($CDCl_3$) 1.67 (9h, s, $C(CH_3)_3$); 2.60 (4H, m, piperazinyl CH_2); 3.61 (4H, m, piperazinyl CH_2); 3.67 (2H, s CH_2); 6.60 (1H, d, J = 9.4); 7.19 (1H, dd, J = 7.7 and 4.7); 7.44 (1H, d, J = 9.4); 7.55 (1H, s); 8.08 (1H, d, J = 7.7); 8.51 (1H, d, J = 4.7).

Example 3: Preparation of 3-[4-(6-iodopyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine

(a) 3-(N,N-Dimethylaminomethyl)-1H-pyrrolo[2,3-b]pyridine

7-azaindole (5.0 g, 17 mmol), dimethylammonium chloride (3.76 g), and paraformaldehyde (1.40 g) were dissolved in n-butanol (30 mL). The reaction was refluxed for 1 hour where upon cooling to room temperature fluffy white needles crystallized out. These were filtered and washed with butanol (10 mL). The solid was dried in vacuo to a white crystalline solid (6.1 g). A portion of this material (2.0 g) was converted to the free base by dissolving in 20 mL water. Upon the addition of ammonium hydroxide (aqueous, 30%) (2 mL) a white precipitate formed, was filtered, washed with water (5 mL), and dried in vacuo to yield 3-(N,N-dimethylaminomethyl)-1H-pyrrolo[2,3-b]pyridine (2.0 g, 27% yield). δH (300MHz $CDCl_3$) 2.27 (6H, s), 3.61 (2H, s), 7.09 (1H, dd, J = 4.5 and 8.0), 7.28 (1H, s), 8.04 (1H, dd, J = 1.2 and 8.1), 8.32 (1H, dd, J = 1.2 and 4.7), ESMS 176 (MH^+).

(b) 3-[4-(6-iodopyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine

A solution of 1-(6-iodopyridazin-3-yl)-piperazine (150 mg, 0.51 mmol) and 3-(N,N-dimethylaminomethyl)-1H-pyrrolo[2,3-b]pyridine (87 mg, 0.47 mmol) (prepared in example 3(a)) in toluene (3 mL) was heated at reflux for 18 h. The heating was discontinued and the solution allowed to cool to room temperature during which time a pale beige solid precipitated out of solution. The solid was collected by filtration and dried *in vacuo* to yield the title compound as a pale beige solid (162 mg, 82% yield). δH (DMSO-d_6) 3.35 (4H, m, piperazinyl CH_2); 3.55 (4H, m, piperazinyl CH_2); 3.70 (2H, s, CH_2); 7.06 (2H, m); 7.40 (1H, s); 7.67 (1H, d, J = 9.5); 8.07 (1H, d, J = 6.0); 8.21 (1H, d, J = 4.8); 11.48 (1H, br s, NH).

Example 4: Preparation of 1-*t*-butoxycarbonyl-3-[4-(6-trimethylstannylpyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine

A mixture of 1-*t*-butoxycarbonyl-3-[4-(6-iodopyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine (52 mg, 0.1 mmol), hexamethylditin (30 OL, 47 mg, 0.145 mmol), and tetrakis triphenylphosphine palladium (0) (23 mg, 0.02 mmol) in toluene (2 mL) under argon was heated at reflux for 1.5 h during which time the solution darkened to a very dark brown. The heating was discontinued and the mixture allowed to cool to room temperature. The reaction was then filtered through a short pad of celite and the pad washed with ethyl acetate. The solvents were then removed under reduced pressure. The residue was partitioned between ethyl acetate and a saturated aqueous solution of KF (7 mL) for 2h with stirring. The mixture was extracted with dichloromethane (2 x 30 mL). The combined organic layers were then concentrated under reduced pressure to give semi-pure title compound. δH ($CDCl_3$) 0.34 (5H, s, $Sn(CH_3)_3$); 1.66 (9H, s, $C(CH_3)_3$); 2.59 (4H, m, piperazinyl CH_2); 3.66 (4H, m, piperazinyl CH_2); 3.73 (2H, s, CH_2); 6.75 (1H, d, J = 9.5); 7.17 (2H, m); 7.54 (1H, s); 8.08 (1H, d, J = 7.6); 8.51 (1H, d, J = 4.5): ESMS 557.04 (M^+): other impurities consist of PPh_3.

Example 5: Preparation of 3-[4-(6-methoxypyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo-[2,3-b]pyridine

A solution of 1-(6-methoxypyridazin-3-yl)-piperazine (100 mg, 0.515 mmol) and 3-(N,N-dimethylaminomethyl)-1H-pyrrolo[2,3-b]pyridine (87 mg, 0.47 mmol)) (prepared in example 3(a)) in toluene (3 mL) was heated at reflux for 15 h. The heating was discontinued and the solution allowed to cool to room temperature during which time a colourless solid precipitated out of solution. The solid was collected by filtration and dried in vacuo to yield the title compound as a colourless solid (147 mg, 94%). δH ($CDCl_3$) 2.63 (4H, m, piperazinyl CH_2); 3.52 (4H, m, piperazinyl CH_2); 3.75 (2H, s, CH_2); 4.02 (3H,s, OCH_3); 6.81 (1H, d, J = 9.6); 6.99 (1H, d, J = 9.7); 7.09 (1H, dd, J = 4.9 and 7.6); 7.28 (1H, s); 8.10 (1H, d, J = 7.5); 8.32 (1H, d, J = 4.6); 9.62 (1H br s, NH).

Example 6: Preparation of 3-[4-(6-methoxy-5-trimethylstannylpyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine

(a) 1-(6-Methoxy-5-trimethylstannylpyridazin-3-yl)-piperazine

Solid 1-(6-methoxypyridazin-3-yl)-piperazine (146 mg, 0.75 mmol) (prepared according to the procedure of Bossier, J. R. et al. J. Med. Chem. 1963, 6, 541) was added to a cold (-78°C) solution of Lithium diisopropylamide (2M solution in THF, 1.65 mL, 3.31 mmol) in dry THF (15 mL). The resulting orange solution with a colourless precipitate was stirred at -78°C for a further 4 h. To this orange solution was then added a solution of trimethyltin chloride (693 mg, 3.31 mmol) in dry THF (1 mL). The remainder of the trimethyltin chloride was then washed into the flask using a further mL of dry THF. During the addition of the trimethyltin chloride the orange colour fades to result in a pale yellow solution. At this point the cold bath was removed and the solution allowed to warm to room temperature. A saturated aqueous solution of KF as added and the mixture stirred for 1 h. The reaction mixture was extracted with dichloromethane (3x 30 mL) and the combined organic layers were dried over Na_2SO_4, filtered and the solvents removed under reduced pressure. Column chromatography of the residue on silica gel using as eluent 7% MeOH in dichloromethane with 1% triethylamine added gave 1-(6-methoxy-5-trimethylstannylpyridazin-3-yl)-piperazine as a colourless glass (82 mg, 30%). Further elution gave recovered starting material. δH ($CDCl_3$) 0.25 (9H, s, $Sn(CH_3)_3$); 2.97 (4H, m, piperazinyl CH_2); 3.11 (1H, br s, NH); 3.44 (4H, m, piperazinyl CH_2); 3.92 (3H, s, OCH_3); 7.02, (1H, s).

(b) 3-[4-(6-methoxy-5-trimethylstannylpyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine

A solution of 1-(6-methoxy-5-trimethylstannylpyridazin-3-yl)-piperazine (40 mg, 0.109 mmol) (prepared in example 6(a)) and 3-(N,N-dimethylaminomethyl)-1H-pyrrolo[2,3-b]pyridine (18 mg, 0.099 mmol)) (prepared in example 3(a)) in toluene

was heated at reflux for 7.5 h. The heating was discontinued and the solution allowed to cool to room temperature. The solvents were removed and the residue purified by column chromatography using 5% MeOH in dichloromethane with 1% triethylamine added as eluent to give 3-[4-(6-methoxy-5-trimethylstannylpyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine as a colourless glass (50 mg). δH ($CDCl_3$) 0.28 (9H, s, $Sn(CH_3)_3$); 2.61 (4H, m, piperazinyl CH_2); 3.49 (4H, m, piperazinyl CH_2); 3.75 (2H, s, CH_2); 3.97 (3H, s, OCH_3); 7.04 (1H, s); 7.07 (1H, dd, J = 4.6 and 7.9); 7.30 (1H, s); 8.09 (1H, d, J = 7.8); 8.31 (1H, d, J = 4.4); 11.29 (1H, br s, NH): ESMS 489 (M^++1).

Example 7: Preparation of 3-[4-(6-methoxy-5-iodopyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine

(a) 3-Methoxy-4-iodo-6-(1-piperazinyl)-pyridazine

To a solution of lithium diisopropylamide (2.0 M in THF, 0.88 mL, 1.76 mmol) in anhydrous THF (15 mL) at -78°C was added solid 3-methoxy-6-(1-piperazinyl)-pyridazine (155 mg, 0.79 mmol). The suspension was stirred at -78°C for 2 h then a solution of iodine (243 mg, 0.955 mmol) in THF (mL) was added via cannula. The reaction was stirred at -78°C for a further 1h then the cold bath was removed and the reaction allowed to warm to room temp. Water (10 mL) was added and the mixture stirred at room temperature overnight. Dichloromethane was then added (10 mL) and the layers separated. The aqueous layer was extracted with more dichloromethane (2x15 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvents removed under reduced pressure. Column chromatography of the residue on silica gel using 5% MeOH in dichloromethane with 1% added as eluent gave 3-methoxy-4-iodo-6-(1-piperazinyl)-pyridazine as a pale golden oil (22 mg, 6%). Further elution gave recovered starting material (103 mg, 67%).

(b) 3-[4-(6-Methoxy-5-iodopyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine

A mixture of 3-methoxy-4-iodo-6-(1-piperazinyl)-pyridazine (20 mg, 0.063 mmol) and 3-(N,N-dimethylaminomethyl)-1H-pyrrolo[2,3-b]pyridine (11.6 mg, 0.063 mmol)) (prepared in example 3(a)) in toluene (1 mL) was heated at reflux under argon atmosphere for 16h. The heating was discontinued and the solvents removed under reduced pressure. The product was purified by preparative layer chromatography on silica gel using 7% methanol in dichloromethane with 1% ammonia added to give 3-[4-(6-methoxy-5-iodopyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine as a pale golden gum (11.1 mg). δH ($CDCl_3$) 2.61 (4H, m, piperazinyl CH_2); 3.51(4H, m, piperazinyl CH_2); 3.74 (2H, s, CH_2); 4.04 (3H, s, OCH_3); 7.09 (1H, dd, J = 7.9 and 4.6); 7.29 (1H, s); 7.49 (1H, s); 8.10 (1H, d, J = 7.9); 8.32 (1H, d, J = 4.5); 10.29 (1H, br s, NH): ESMS: 451 (M^++1).

Example 8: Preparation of 3-[4-(pyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine

To a solution of 3-chloro-6-(1-piperazinyl)pyridazine (198 mg, 1 mmol) and KOH (61 mg, 1.1 mmol) in methanol (10 mL) under an inert atmosphere was added Palladium on activated charcoal (10% Pd on charcoal, 20 mg, 10% by weight). The reaction was then placed under an atmosphere of hydrogen and stirred at room temperature for 1.5 h. The mixture was then filtered through a short pad of celite and the solvents removed under reduced pressure. The crude reaction mixture was then dissolved in toluene and 3-(N,N-dimethylaminomethyl)-1H-pyrrolo[2,3-b]pyridine (160 mg, 0.9 mmol)) (prepared in example 3(a)) was added. The mixture was heated at reflux overnight (20 h) then allowed to cool to room temperature. The solid was filtered off and dried in vacuo to yield the title compound as a colourless solid (273 mg, 92% yield). δH (DMSO-d6) 2.51 (4H, m, piperazinyl CH2), 3.56 (4H, m, piperazinyl CH2), 3.69 (2H, s, CH2), 7.06 (1H, dd, J = 4.8 and 7.8), 7.22 (1H, d, J = 9.2), 7.35 (1H, dd, J = 4.4 and 9.2), 7.41 (1H, s), 8.07 (1H, d, J = 7.8), 8.21 (1H, d, J = 4.4), 8.54 (1H, d, J = 4.8), 11.55 (1H, br s, NH).

Example 9: Preparation of ^{123}I-3-[4-(6-iodopyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine

To a vial of sodium ^{123}I iodide in sodium hydroxide was added in the following order: 20 μL of 1N HCl, 300-400 μg 1-*t*-butoxycarbonyl-3-[4-(6-trimethylstannyl-pyridazin-3-yl)-piperazin-1-yl]methylpyrrolo[2,3-b]pyridine in 100 μL ethanol, and 50 μg Chloramine T in 50 μL of distilled water. This mixture was swirled for 30 seconds and let stand at room temperature for 1 h. At this point the reaction mixture was neutralized and the product extracted into dichloromethane. Analysis and purification of the compound was carried out by HPLC on reverse phase C18 silica column using a gradient of 0 to 90% acetonitrile in water containing 0.1% trifluoroacetic acid over 20 min. The labeled ^{123}I-3-[4-(6-iodopyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine eluted with a retention time of 9.4 minutes and was shown to be the correct compound by coinjection with a reference sample of nonradioactive 3-[4-(6-iodopyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine.

Using the above procedure and replacing sodium ^{123}I iodide with sodium ^{125}I iodide, ^{125}I-3-[4-(6-iodopyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine

Example 10: Preparation of 3-[4-(6-methylpyridazin-3-yl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine

(a) 6-Methyl-3-piperazin-1-yl-pyridazine

3-Methyl-6-chloro-pyridazine (128.5 mg, 1 mmol) was mixed with piperazine (860 mg, 10 mmol) in a 4-mL glass vial and heated in a sand bath at 180°C for 3 h. The reaction mixture was cooled to room temperature and dissolved in 2 mL of distilled water. The aqueous solution was extracted 3 times with 3 mL of dichloromethane. The combined extracts were dried with anhydrous Na_2SO_4 and

evaporated in vacuo. A tan cloured product was obtained (130 mg, 61% yield) and used without further purification.

$C_9H_{14}N_4$ MW: 178.24; MS: 178.86; NMR: δ($CDCl_3$, 300MHz): 2.35 (1H, s); 2.53 (3H, s); 3.01 (4H, m); 3.58 (4H, m); 6.83 (1H, d, J=9.3); 7.08 (1H, d, j=9.4).

(b) 3-[4-(6-methylpyridazin-3-yl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine

3-Methyl-6-piperazin-1-yl-pyridazine (162 mg, 0.88 mmol) and 3-dimethylamino-methyl-7-azaindole (120 mg, 0.69 mmol) were suspended in 3 mL of toluene and heated under reflux for 16 h. The reaction mixture was cooled to room temperature and the precipitated reaction product was filtered off. 148 mg (71% yield) of the tan coloured compound was obtained. $C_{17}H_{20}N_6$ MW: 308.39; MS: 308.99; NMR: δ(DMSO-d_6, 300MHz): 2.42 (3H, s); 3.35 (4H, br s); 3.51 (4H, br s); 3.72 (2H, s); 7.07 (1H, dd, J=4.4 and 7.8); 7.17 (1H, d, J=9.4); 7.25 (1H, d, J=9.4); 7.41 (1H, s); 8.08 (1H, d, J=7.7); 8.21 (1H, d, J=4.2).

Example 11: Synthesis of 3-[4-(6-iodo-5-methylpyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine

To a solution of 3,6-dichloro-4-methylpyridazine (163 mg) in acetonitrile (6 mL) was added piperazine (90.4 mg, 1.05 mmol). The mixture was heated at reflux for 4 h then allowed to cool, and the solvents removed. CH_2Cl_2 was added and the mixture triturated then filtered off. The residue was washed with CH_2Cl_2 and dried in vacuo to give 6-(1-piperazinyl)-3-chloro-4-methylpyridazine hydrochloride as a white solid (150 mg, 62%).

To a solution of 6-(1-piperazinyl)-3-chloro-4-methylpyridazine hydrochloride (106 mg, 0.425 mmol) and sodium acetate (58 mg, 0.425 mmol) in water (300 OL) was added acetic acid (500 OL), followed by formaldehyde solution (37% in water)

and the reaction stirred at room temperature for 10 min. To this mixture was then added 7-azaindole (50.2 mg, 0.425 mmol) and the reaction mixture stirred at room temperature for 15h. Water (200 OL) was then added to the reaction and the whole mixture transferred to a larger vial. Saturated ammonium chloride solution (500 OL) was added and the mixture extracted with CH_2Cl_2 (1 mL). The organic extracts were dried over $MgSO_4$, filtered and the solvents removed under reduced pressure to give a pale beige solid. A portion of this solid was purified by PLC on silica (eluting with 14% MeOH in CH_2Cl_2 with 1% ammonia added) to give the title compound as a white solid (4 mg). δH (300MHz, $CDCl_3$) 2.2 (3H, s), 2.62 (4H, m, piperazinyl), 3.62 (4H, m, piperazinyl), 3.75 (2H, s), 6.75 (1H, s), 7.10 (1H, dd, J = 4.7 and 7.9), 7.28 (1H, s), 8.10 (1H, d, J = 7.8), 8.32 (1H, d, J = 4.3); ESMS 339 (MH^+).

Example 12: 3-[4-(6-hydroxypyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine

To a solution of 3-(1-piperazinyl)-6-hydroxypyridazine (89 mg, 0.48 mmol) (prepared according to the procedure of *Eur. J. Med. Chem.* **1992**, *27*, 545) in toluene (2 mL) was added 3-(N,N-dimethylaminomethyl)-1H-pyrrolo[2,3-b]pyridine (95 mg, 0.53 mmol)) (prepared in example 3(a)). The mixture was then heated at reflux for 16 h and heating discontinued. The resulting precipitate was filtered off and dried in vacuo to give the title compound as a colourless solid (119 mg, 77%). δH (DMSO-d_6) 2.48 (4H, br m, piperzinyl protons), 3.18 (4H, br m , piperzinyl protons), 3.68 (2H, s), 6.76, (1H, d, J = 10.1), 7.06 (1H, dd, J = 5.1 and 7.7), 7.39 (1H, s), 7.48 (1H, d, J = 10.2), 8.05 (1H, d, J = 7.8), 8.20 (1H, d, J = 4.7), 11.5 (1H, br s), 12.08 (1H, br s); ESMS 311 (MH^+).

Example 13: 3-[4-(6-trifluoromethanesulfonyloxypyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine

To a solution of 3-[4-(6-hydroxypyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo-[2,3-b]pyridine (20 mg, 0.065 mmol) in pyridine (0.5 mL) at room temperature was added trifluoromethanesulfonic anhydride (16 mL, 0.097 mmol) via syringe over 2 min. (giving an orange solution). The reaction was stirred at room temperature for a further 3 h and then water (3 mL) was added. The mixture was extracted with CH_2Cl_2 three times. The combined organics were dried over $MgSO_4$, filtered and the solvents removed under reduced pressure. Column chromatography of the residue on silica gel using 10% EtOH in CH_2Cl_2 as eluent gave the title compound as a pale yellow solid (9 mg, 32%). δH (300MHz, $CDCl_3$) 2.59 (4H, br m, piperazinyl protons), 3.68 (4H, br m, piperazinyl protons), 3.74 (2H, s), 7.02 (1H, dd, J = 4.9 and 7.9), 7.25 (2H, ap q, J = 9.7, pyridazinyl protons), 7.67 (1H, s), 8.05 (1H, d, J = 7.6), 8.24 (1H, d, J = 4.7), 10.97 (1H, br s); ESMS 443 (MH^+).

Example 14: 3-[4-(6-phenylpyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine

A mixture of piperazine (4.5 g, 52.6 mmol) and 3-chloro-6-phenylpyridazine (1g, 5.26 mmol) and EtOH (0.5 mL) were heated together at 170°C for 2 h then heating was discontinued. The resulting solid was partitioned between H_2O and CH_2Cl_2 and the layers separated. The aqueous layer was further extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered and the solvents removed under reduced pressure. Column chromatography of the residue on silica gel using 20% EtOH in CH_2Cl_2 with 1% Et_3N added gave 3-(1-piperazinyl)-6-phenylpyridazine as a colourless solid (1.04 g, 82%).

To a solution of 3-(1-piperazinyl)-6-phenylpyridazine (100 mg, 0.42 mmol) in toluene (2 mL) was added 3-(N,N-dimethylaminomethyl)-1H-pyrrolo[2,3-b]pyridine

(66 mg, 0.37 mmol)) (prepared in example 3(a)). The mixture was heated at reflux for 16 h and then heating was discontinued. The resulting colourless precipitate was filtered off and then dried in vacuo to give the title compound as colourless solid (128 mg, 92%). ΔH (300MHz, DCl in D_2O) 2.83 (2H, t, J = 11.6), 2.96 (2H, t, J = 13.2), 3.17 (2H, d, J = 11.8), 3.97 (2H, d, J = 14.4), 4.15 (2H, s), 6.96 (3H, m, Ph), 7.05 ((1H, dd, J = 8.6 and 5.9), 7.19 (2H, d, J = 7.6), 7.40 (1H, d, J = 9.8), 7.42 (1H, s), 7.71 (1H, d, J = 9.9), 7.84 (1H, d, J = 5.9), 8.29 (1H, d, J= 8.0) ;ESMS 371 (MH^+).

Example 15: 3-[4-(3,5-dichloropyridin-2-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine

A solution of piperazine (180 mg, 2.1 mmol), 2,3,5-trichloropyridine (364.5 mg, 2.0 mmol) and Na_2CO_3 (1.06 g, 10 mmol) in acetonitrile (10 mL) was heated at reflux for 20 h then allowed to cool and filtered (CH_2Cl_2 washing). The solvents were removed and the residue purified by column chromatography on silica gel (10% EtOH in CH_2Cl_2 with 1% Et_3N added) to give 2-(1-piperazinyl)-3,5-dichloropyridine as a colourless solid (265 mg, 57%). ΔH (300MHz, $CDCl_3$) 3.02 (4H, m, piperazinyl protons), 3.27 (4H, m, piperazinyl protons), 7.56 (1H, d, J = 2.2), 8.10 (1H, d, J = 2.2).

To a solution of 2-(1-piperazinyl)-3,5-dichloropyridine (243 mg, 1.05 mmol) in toluene (5 mL) was added 3-(N,N-dimethylaminomethyl)-1H-pyrrolo[2,3-b]pyridine (175 mg, 1.0 mmol)) (prepared in example 3(a)). The mixture was heated at reflux for 7 h and then allowed to cool whereupon a pale beige solid crystallized out of the mixture. The solid was filtered off and dried in vacuo. This was further purified by column chromatography on silica gel using 5% MeOH in CH_2Cl_2 with 1% Et_3N added as eluent to give the title compound as a pale beige solid (310 mg, 86%). δH (300MHz, DMSO-d_6) 2.64 (4H, m, piperazinyl protons), 3.35 (4H, m, piperazinyl

protons), 3.77 (2H, s), 7.10 (1H, dd, J = 4.8 and 7.8), 7.28 (1H, d, J = 7.7), 7.56 (1H, s), 8.10 (1H, s), 8.12 (1H, d, J = 7.0), 8.32 (1H, d, J = 4.6); ESMS 362 (MH^+).

Example 16: Preparation of 3-[4-(pyridin-2-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine

To a solution of 3-(N,N-dimethylaminomethyl)-1H-pyrrolo[2,3-b]pyridine (258 mg, 1.39 mmol)) (prepared in example 3(a)) in toluene (10 mL) was added 1-(pyridin-2-yl)piperazine (233 mL, 250 mg, 1.53 mmol). The mixture was heated at reflux over night. Heating was discontinued and when the reaction temperature had reached room temperature the solid was filtered off and dried in vacuo to give the title compound as a colourless solid (395 mg, 93%). δH (300 MHz, $CDCl_3$) 2.50 (4H, m, piperazinyl), 3.46 (4H, m, piperazinyl), 3.68 (2H, s), 6.61 (1H, dd, J = 5.1 and 6.9), 6.78 (1H, d, J = 8.6), 7.06 (1H, dd, J = 4.7 and 7.8), 7.39 (1H, s), 7.51 (1H, dd, 6.9 and 8.6), 8.10 (1H, d, J = 8.1), 8.12(1H, d, J = 7.8), 8.22(1H, d, J = 4.6), 11.49(1H, br s); ESMS 294 (MH^+).

Example 17: Preparation of 3-[4-(5-iodopyridin-2-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine

(a) 2-Chloro-5-iodopyridine

To a suspension of 5-amino-2-chloropyridine (2.56 g, 20 mmol) and hydriodic acid (57% solution in water, 6.8 mL) in dichloromethane (50 mL) at 0°C was added $NaNO_2$ portionwise over 2 min. The reaction was then stirred at 0°C for a further 30 min and then poured into a mixture of dichloromethane and saturated sodium thiosulphate solution and the organic layer separated. The aqueous layer was extracted further with dichloromethane (2x 50 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and the solvents removed under reduced

pressure. Column chromatography of the residue on silica gel (dichloromethane as eluent) gave 2-chloro-5-iodopyridine as a colourless solid (930 mg, 20%). δH (300MHz, $CDCl_3$) 7.10 (1H, d, J = 8.3), 7.88 (1H, dd, J = 2.4 and 8.2), 8.55 (1H, d, J = 2.0), ESMS 239 (MH^+).

(b) 1-(5-Iodopyridin-2-yl)-piperazine

To a solution of piperazine (215 mg, 2.5 mmol) and potassium carbonate (890 mg, 6.45 mmol) in acetonitrile (5 mL) was added 2-chloro-5-iodopyridine (300 mg, 1.25 mmol) (prepared above). The mixture was heated at reflux for 26 h and allowed to cool. It was then filtered and the solvents removed under reduced pressure. Column chromatography of the residue on silica gel (dichloromethane:methanol:ammonia solution 100:5:1) gave 1-(5-iodopyridin-2-yl)-piperazine as a yellow solid (215 mg, 60%). δH (300MHz DMSO-d_6) 2.76 (4H, m, piperazinyl), 3.40 (4H, m, piperazinyl), 6.72 (1H, d, J=9.0), 7.77 (1H, dd, J=2.4 and 9.0), 8.25 (1H, d, J=2.4), ESMS 290 (MH^+).

(c) 3-[4-(5-Iodopyridin-2-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine

To a solution of 1-(5-iodopyridin-2-yl)-piperazine (100 mg, 0.34 mmol) in toluene (2 mL) (prepared above) was added 3-(N,N-dimethylaminomethyl)-1H-pyrrolo[2,3-b]pyridine (58 mg, 0.32 mmol)) (prepared in example 3(a)). The mixture was heated at reflux over night and then allowed to cool to room temperature. The resulting solid was filtered and dried in vacuo to give 3-[4-(5-iodopyridin-2-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine as a colourless solid (118 mg, 79%). δH (300MHz DMSO-d_6) 2.47 (4H, m, piperazinyl), 3.45 (4H, m, piperazinyl), 3.68 (2H, s), 6.71 (1H, d, J = 9), 7.05 (1H, dd, J = 4.8 and 7.9), 7.39 (1H, s), 7.75 (1H, d, J = 8.8), 8.06 (1H, d, J = 7.8), 8.21 (1H, d, J = 4.5), 8.23 (1H, s), 11.51 (1H, br s, NH).

Example 18: Preparation of 3-[4-(5-bromopyridin-2-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine

(a) (5-Bromopyridin-2-yl)-piperazine

A solution of 2,5-dibromo piperazine (1.59 g, 8 mmol), and piperazine(1.45 g, 16 mmol), and potassium carbonate (6 g) in acetonitrile (50 mL) was heated at reflux for 48 h. The heating was discontinued and the solution allowed to cool to room temperature. The solid was filtered off and washed with acetonitrile (50 mL). The organics were concentrated to a tan solid. The product was purified by column chromatography on silica gel using dichloromethane:methanol:triethylamine (94:5:1) as eluent to provide (5-bromopyridin-2-yl)-piperazine as an off-white solid (1.75 g, 95%). δH (300MHz $CDCl_3$) 1.75 (1H, br s), 2.95 (4H, m, piperaziny), 3.45 (4H, m, piperazinyl), 6.52 (1H, d, J = 9.0), 7.51 (1H, dd, J = 2.5 and 9.0), 8.17 (1H, d, J = 2.4), ESMS 243 (MH^+).

(b) 3-[4-(5-Bromopyridin-2-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine

A solution of 1-(5-bromopyridin-2-yl)-piperazine (310 mg,1.28 mmol) (prepared above) and 3-(N,N-dimethylaminomethyl)-1H-pyrrolo[2,3-b]pyridine (215 mg, 1.16 mmol) in toluene (10 mL) was heated at reflux for 18 h. The heating was discontinued and the solution allowed to cool to room temperature during which time a colourless solid precipitated out of solution. The solid was collected by filtration and dried in vacuo to yield 3-[4-(5-bromopyridin-2-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine as a colourless solid (420 mg, 97%). δH (300MHz $CDCl_3$) 2.58 (4H, m, piperazinyl), 3.51 (4H, m, piperazinyl), 3.75 (2H, s), 6.50 (1H, d, J = 9.0), 7.09 (1H, dd, J = 5.0 and 7.9), 7.27 (1H, s), 7.49 (1H, dd, J = 2.6 and 9.0), 8.10 (1H, d, J = 7.8), 8.17 (1H, d, J = 2.3), 8.32 (4.5), 9.69 (1H , br s) ESMS 374 (MH^+).

Example 19: Preparation of 1-t-butoxycarbonyl-3-[4-(5-bromopyridin-2-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine

To a solution of 3-[4-(5-bromopyridin-2-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine (200 mg, 0.54 mmol) and KOH (91 mg, 1.6 mmol) in dichloromethane (2 mL) at room temperature was added di-tert-butyldicarbonate (130 mg, 0.59 mmol). The mixture was stirred at room temperature for 4 h and was then filtered. The residue was washed with dichloromethane and the solvents removed under reduced pressure. The resulting residue was purified by column chromatography on silica gel using ethyl acetate:dichloromethane 7:3 as eluent to give the title compound as a colourless foam (230 mg, 91%). δH (300MHz $CDCl_3$) 1.67 (9H, s); 2.58 (4H, m, piperazinyl); 3.51 (4H, m, piperzinyl); 3.6 (2H, s); 6.52 (1H, d, J = 9.0); 7.19 (1H, dd, J = 4.6 and 7.5); 7.51 (1H, dd, J = 2.5 and 9.0); 7.54 (1H, s); 8.09 (1H, d, J = 7.9); 8.18 (1H, d, J = 2.5); 8.51 (1H, d, J = 4.2)ESMS 472 (MH^+).

Example 20: Preparation of 1-t-butoxycarbonyl-3-[4-(5-trimethylstannylpyridin-2-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine

A mixture of 1-t-butoxycarbonyl-3-[4-(5-bromopyridin-2-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine (35 mg, 0.074 mmol), hexamethylditin (40 OL, 63 mg, 0.193 mmol), and tetrakis(triphenylphosphine) palladium (0) (25 mg, 0.022 mmol) in toluene (5 mL) under argon was heated at reflux for 3 h during which time the solution darkened to a very dark brown. Another portion of tetrakis(triphenylphosphine) palladium (0) (13 mg, 0.01 mmol) was added and the reaction refluxed for 5 h further. The heating was discontinued and the mixture allowed to cool to room temperature. The reaction was then filtered through a short pad of celite and the pad washed with ethyl acetate. The solvents were then removed under reduced pressure. The resulting black residue was purified by preparatory silica plate using ethyl acetate as eluent to give the semi-pure title

compound as a colorless glass (20 mg, 48%). δH (300MHz $CDCl_3$) 0.24 (9H, s, trimethylstannyl), 1.65 (9H, s, t-butoxycarbonyl), 2.56 (4H, m, piperazinyl), 3.52 (4H, m, piperazinyl), 3.64 (2H, s, CH_2), 6.61 (1H, d, J=8.3), 7.16 (1H, dd, J=4.8 and J=7.7), 7.43 (1H, m), 7.50 (1H, s), 8.16 (1H, s), 8.48 (1H, d, J=4.6), ESMS 558 (MH^+).

Example 21: Preparation of ^{123}I-3-[4-(5-iodopyridin-2-yl)-piperazin-1-yl]methylpyrrolo-[2,3-b]pyridine

To a vial of sodium ^{123}I iodide in sodium hydroxide was added in the following order: 20 μL acetic acid, 300-400 μg 1-*t*-butoxycarbonyl-3-[4-(5-trimethylstannyl-pyridin-2-yl)-piperazin-1-yl]methylpyrrolo[2,3-b]pyridine in 100 μL ethanol, and 50 μg Chloramine T in 50 μL of distilled water. This mixture was swirled for 30 seconds and let stand at room temperature for 40 min. 20μL 1N HCl was added and the reaction was let stand at room temperature for 30 min. Analysis and purification of the compound was carried out by HPLC on reverse phase C18 silica column using a gradient of 0 to 90% acetonitrile in water containing 0.1% trifluoroacetic acid over 20 min. The labeled ^{123}I-3-[4-(5-iodopyridin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine eluted with a retention time of 11.2 minutes and was shown to be the correct compound by coinjection with a reference sample of nonradioactive 3-[4-(5-iodopyridin-2-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine.

Using the above procedure and replacing sodium ^{123}I iodide with sodium ^{125}I iodide, ^{125}I-3-[4-(5-iodopyridin-2-yl)-piperazin-1-yl]methylpyrrolo[2,3-b]pyridine can be prepared.

Example 22: 3-[4-(6-bromopyridin-2-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine

To a solution of piperazine (725 mg, 8.43 mmol) and 2,6-dibromopyridine (1 g, 4.22 mmol) in acetonitrile (20 mL) was added K_2CO_3 (2.91 g, 21.1 mmol). The mixture was heated at reflux for 48 h and then allowed to cool to room temperature. The mixture was filtered and the solvents removed. Column chromatography of the residue on silica gel using 7% EtOH in CH_2Cl_2 with 1% Et_3N added gave 2-(1-piperazinyl)-6-bromopyridine as a thick oil which slowly crystallized (820 mg, 85%). ΔH (300MHz, $CDCl_3$) 2.93 (4H, m, piperazinyl protons), 3.49 (4H, br m, piperazinyl protons)6.48 (1H, d, J = 8.3), 6.72 (1H, d, J = 7.5), 7.26 (1H, dd, J = 8.0 and 7.6)

To a solution of 2-(1-piperazinyl)-6-bromopyridine (300 mg, 1.3 mmol) in toluene (15 mL) was added 3-(N,N-dimethylaminomethyl)-1H-pyrrolo[2,3-b]pyridine (206 mg, 1.18 mmol)) (prepared in example 3(a)). The mixture was heated at reflux for 14 h then the heating was discontinued. When the reaction mixture had cooled to room temperature the solid precipitate was filtered off and dried in vacuo to give the title compound as a colourless solid (220 mg, 47%); δH (300MHz, DMSO-d_6) 2.47 (4H, br m, piperazinyl protons), 3.46 (4H, br m, piperzinyl protons), 3.67 (2H, s), 6.79 (1H, d, J = 7.7), 6.80 (1H, d, J = 7.8), 7.05 (1H, dd, J = 4.7 and 7.8), 7.39 (1H, s), 7.42 (1H, d, J = 7.8), 8.06 (1H, d, J = 7.8), 8.21 (1H, d, J = 4.5)11.52 (1H, br s); ESMS 372 (MH^+).

Example 23: 3-[4-(6-methoxypyridin-2-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine

A mixture of 2-chloro-6-methoxypyridine (1 g, 6.99 mmol), piperazine (6.01 g, 69.9 mmol) and EtOH (0.5 mL) were heated at 170°C under reflux conditions for 2 h then the reaction was allowed to cool. Column chromatography of the residue (5% EtOH in CH_2Cl_2 with 1% Et_3N added) gave 2-(1-piperazinyl)-6-methoxypyridine as a thick oil (695 mg, 51%). ΔH (300MHz, $CDCl_3$) 2.98 (4H, m, piperazinyl protons), 3.47 (4H, m, piperazinyl protons), 3.85 (3H, s), 6.05 (1H, d, J = 8.0), 6.13 (1H, d, J = 7.9), 7.38 (1H, app t, J = 7.8 and 8.0)

A solution of 2-(1-piperazinyl)-6-methoxypyridine (200 mg, 1.03 mmol) and 3-(N,N-dimethylaminomethyl)-1H-pyrrolo[2,3-b]pyridine (164 mg, 0.94 mmol)) (prepared in example 3(a)) in toluene (2 mL) was heated at reflux for 16 h then allowed to cool, where upon a precipitate crystallised out of solution. The solid was filtered off and dried in vacuo to give the title compound as a colourless solid (134 mg, 44%); δH (300MHz, DMSO-d_6) 2.50 (4H, m, piperazinyl protons), 3.45 (4H, m, piperazinyl protons), 3.69 (2H, s), 3.75 (3H, s), 6.01 (1H, d, J = 7.9), 6.26 (1H, d, J = 8.1), 7.06 (1H, dd, J = 4.6 and 7.9), 7.39 (1H, s), 7.43 (1H, d, J = 7.9), 8.06 (1H, d, J = 7.6), 8.20 (1H, d, J = 4.5), 11.49 (1H, s); ESMS 324 (MH^+).

Example 24: 3-[4-(5-trifluoromethylpyridin-2-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine

A mixture of piperazine (4.74 g, 55 mol) and 2-chloro-5-trifluoromethylpyridine (1 g, 5.5 mmol) and EtOH (0.5 mL) was heated at 170°C under reflux conditions for 2 h then allowed to cool. The solid was then partitioned between H_2O and CH_2Cl_2 and the layers separated. The aqueous layer was then further extracted with CH_2Cl_2 and the combined organic extracts were dried over $MgSO_4$, filtered and the solvents removed under reduced pressure. Column chromatography of the residue on silica gel (10% EtOH in CH_2Cl_2 with 1% Et_3N added as eluent) gave 2-(1-piperazinyl)-5-trifluoromethylpyridine as a pale yellow oil (1.21 g, 95%).

To a solution of 2-(1-piperazinyl)-5-trifluoromethylpyridine (200 mg, 0.86 mmol) in toluene (2 mL) was added 3-(N,N-dimethylaminomethyl)-1H-pyrrolo[2,3-b]pyridine (137 mg, 0.78 mmol)) (prepared in example 3(a)). The mixture was heated at reflux for 15 h and then allowed to cool to room temperature whereupon a solid precipitated out of solution. The solid was filtered off and dried in vacuo to give the title compound as a colourless solid (236 mg, 84%). δH (300MHz, DMSO-d_6) 2.48 (4H, m, piperazinyl protons), 3.61 (4H, m, piperazinyl protons), 3.68 (2H, s), 6.92 (1H, d, J = 9.1), 7.05 (1H, dd, J = 4.6 and 7.8), 7.39 (1H, s), 7.74 (1H, dd, J =

2.1 and 6.9)8.06 (1H, d, J = 7.6), 8.22 (1H, d, J = 4.1), 8.39 (1H, s), 11.52 (1H, s); ESMS 362 (MH^+).

Example 25: Receptor Binding Affinities

D2 and D4 receptor-binding affinities of the compounds prepared in Examples 1, 2 and 3 were evaluated as described in Grandy et al., 1989, Proc. Natl. Acad. Sci, *86*:9762-9766 and Van Tol et al, 1992, Nature, *358*:149-152 (the disclosures of which are hereby incorporated by reference) for their ability to reduce binding of ^{3}H-spiperone as compared to the reference compound clozapine. The potency of the test compound to reduce ^{3}H-spiperone binding is directly correlated to its binding affinity for the receptor.

The test compounds were assayed at a range of concentrations and the % inhibition of ^{3}H-spiperone binding at each test concentration was measured. Specific binding in the absence of test compound is the difference of total binding minus non-specific binding and similarly specific binding (in the presence of test compound) is the difference of displacement binding minus non-specific binding. An inhibition response curve was used to determine the IC_{50} of the test compound 3-[4-(5-iodopyridin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine. Ki was calculated by the Cheng and Prustoff transformation:

$$Ki = IC_{50} / (1 + [L]/K_D)$$

where [L] is the concentration of ^{3}H-spiperone used in the assay and K_D is the dissociation constant of ^{3}H-spiperone determined independently under the same binding conditions.

Assay results (Ki) are reported in the following Table 1, and % inhibition of ^{3}H-spiperone binding at 10 nM of various test compounds are reported in Table 2. These results show clearly the D4 selectivity of compounds of the invention. The compound 3-[4-(4-iodophenyl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine was prepared as described in Pollak et al., US patent 5,725,838 issued March 10, 1998.

Table 1:

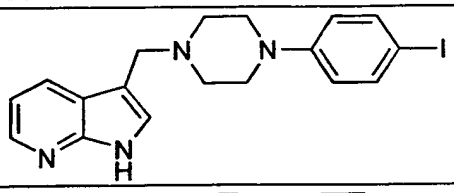
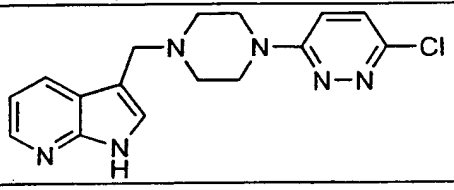
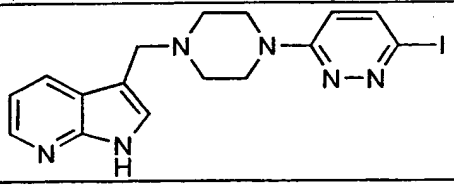
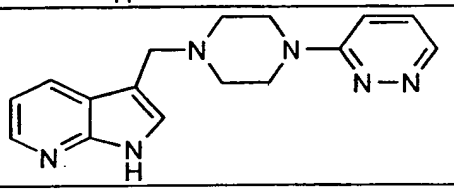
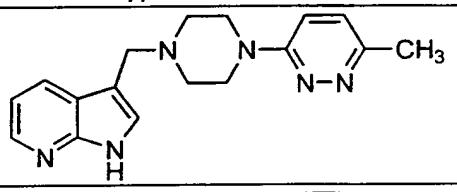
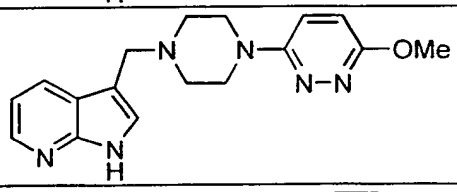
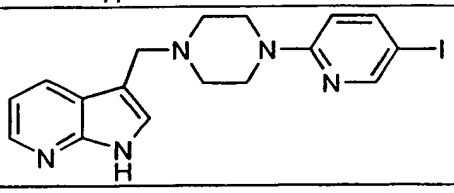
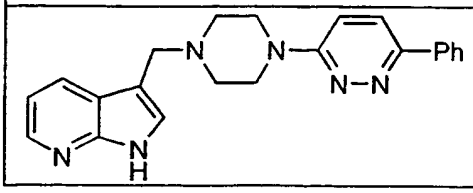
Structure	D4 Affinity	D2 Affinity
	0.73 nM	676 nM
	2.9 nM	9529 nM
	0.92 nM	2610 nM
	31.2 nM	>10 OM
	4.3 nM	>5000 nM
	<10 nM	>10 OM
	1.0 nM	3655 nM

Table 2:

Structure	% Inhibition of Binding to D4 at 10 nM	% Inhibition of Binding D2 at 10 nM
	40	10

Alternatively, the D2 and D4 receptor-binding affinities of the compounds of the invention can be evaluated as described in WO95/17400 (the disclosure of which is hereby incorporated by reference) for their ability to reduce binding of 3H-spiperone as compared to the reference compound clozapine. The potency of the test compound to reduce 3H-spiperone binding is directly correlated to its binding affinity for the receptor.

Briefly, the D4 receptor is utilised in the form of membrane preparations obtained from HEK 298 cells stably transfected with human D4 receptor (D4.2 sub-type). D2 receptor is utilised in the form of membrane preparations obtained from GH4C1 (rat pituitary) cells stably transfected with the human D2 receptor (short isoform). The total spiperone binding assay is started by the addition of 500 mL (50 mg protein) membrane homogenate to a solution of 900 mL incubation buffer and 100 mL (0.25 nM final conc.) 3H-spiperone. The binding reaction is stopped and the samples are filtered under vacuum and the filters are then washed 3 times with 5 mL ice cold 50 mmol Tris buffer (pH 7.4). Individual filter disks are put in scintillation vials (Biovials, Beckman). Ready Protein Plus liquid scintillant (5 mL, Beckman) is added and the vials counted by liquid scintillation spectrophotometry (Beckman LSC 6500) after equilibrating for three hours at room temperature to determine total binding (BT).

Non-specific binding for D4 is assayed by incubating membrane homogenate, 3H-spiperone and fresh dopamine. Filtrate is counted using the same procedure as in the total binding assay described above to give the non-specific binding value (NSB).

Non-specific binding for D2 is similarly assessed, with the exception that (-)-sulpiride is used in place of dopamine.

To assess displacement, membrane homogenate is incubated with ^{3}H-spiperone and test compound dissolved in DMSO. Filtrate is counted using the same procedure as in the total binding assay described above, to give the displacement binding value (B_D).

The test compounds are assayed at a range of concentrations chosen such that the middle dose would cause about 50% inhibition of ^{3}H-spiperone binding. Specific binding in the absence of test compound (B_0) is the difference of total binding (B_T) minus non-specific binding (NSB) and similarly specific binding (in the presence of test compound) (B) is the difference of displacement binding (B_D) minus non-specific binding (NSB). IC_{50} is determined from an inhibition response curve, logit-log plot of $\%B/B_0$ vs concentration of test compound, and Ki can be calculated from this using the Cheng and Prustoff transformation as described above.

Example 26:

The aim of this study was to assess the affinity of four compounds for the various receptors shown in table 3 in a radioligand binding assay. The compounds were tested for binding to the various receptors according to the method described in the reference cited in table 3.

Table 3

Receptor	Tissue	Reference Compound	Reference
α2A	Human recombinant (Sf9 cells)	yohimbine	Devedjian et al. (1994). Eur. J. Pharmacol., 115: 622-628
β1	Human recombinant (Sf9 cells)	atenolol	Abrahamsson et al. (1988). Biochem. Pharmacol., 37: 203-208
β2	Human recombinant (Sf9 cells)	ICI 118551	Abrahamsson et al. (1988). Biochem. Pharmacol., 37: 203-208
D1	Human recombinant cells)	SCH 23390	Zhou et al. (1990). Nature, 347: 76-80
D3	Human recombinant (CHO cells)	(+)butaclamol	MacKenzie et al. (1994). Eur. J. Pharmacol., 266: 79-85
D5	Human recombinant (GH4 cells)	SCH 23390	Sunahara et al. (1991). Nature, 350: 614-619
M1	Human recombinant (CHO cells)	pirenzepine	Dorje et al. (1991). J. Pharmacol. Exp. Ther., 256: 727-733
M2	Human recombinant (CHO cells)	methoctramine	Dorje et al. (1991). J. Pharmacol. Exp. Ther., 256: 727-733
M3	Human recombinant (CHO cells)	4-DAMP	Dorje et al. (1991). J. Pharmacol. Exp. Ther., 256: 727-733
5-HT1A	Human recombinant (CHO cells)	8-OH-DPAT	Mulheron et al. (1994). J. Biol. Chem., 269: 12954-12962
5-HT1B	Rat cerebral cortex	serotonin	Hoyer et al. (1985). Eur. J. Pharmacol., 118: 1-12
5-HT2A	Human recombinant (CHO cells)	ketanserin	Bonhaus et al. (1995). Brit. J. Pharmacol., 115: 622-628
5-HT2C	Human recombinant (CHO cells)	mesulergine	Bonhaus et al. (1995). Brit. J. Pharmacol., 115: 622-628
5-HT3	N1E-115 cells	MDL 72222	Hoyer & Neijt (1988). Mol. Pharmacol., 33: 303-309

The following four compounds were tested at a concentration of 1 OM under the experimental conditions shown in table 4:

Compound A: 3-[4-(4-iodophenyl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

Compound B: 3-[4-(5-iodopyridin-2-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

Compound C: 3-[4-(6-iodopyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;

Compound D: 3-[4-(6-methylpyridazin-3-yl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine.

Table 4: Experimental Conditions

Receptor	Radioligand and concentration	Non-specific ligand and concentration	Incubation conditions
α2A	[3H]RX821002 (1.5 nM)	(-)epinephrine (100 OM)	60 min/22°C
β1	[3H](-)CGP 12177 (0.15 nM)	alprenolol (50 OM)	60 min/22°C
β2	[3H](-)CGP 12177 (0.15 nM)	alprenolol (50 OM)	30 min/22°C
D1	[3H]SCH 23390 (0.3 nM)	SCH 23390 (10 OM)	60 min/22°C
D3	[3H]spiperone (0.3 nM)	(+)butaclamol (10 OM)	60 min/22°C
D5	[3H]SCH 23390 (0.3 nM)	SCH 23390 (10 OM)	60 min/22°C
M1	[3H]pirenzepine (2 nM)	atropine (1 OM)	60 min/22°C
M2	[3H]AF-DX 384 (2 nM)	atropine (1 OM)	60 min/22°C
M3	[3H]4-DAMP (0.5 nM)	atropine (1 OM)	60 min/22°C
5-HT1A	[3H]8-OH-DPAT (0.3 nM)	8-OH-DPAT (10 OM)	60 min/22°C
5-HT1B	[125I]CYP (0.1 nM)	serotonin (10 OM)	90 min/37°C
5-HT2A	[3H]ketanserin (2 nM)	ketanserin (1 OM)	15 min/37°C
5-HT2C	[3H] mesulergine (0.7 nM)	mesulergine (1 OM)	30 min/37°C
5-HT3	[3H]BRL 43694 (1 nM)	metoclopramide (100 OM	180 min/4°C

Following incubation, membranes or cells in suspension were rapidly filtered under vacuum through GF/B or GF/C glass fiber filters (Packard). The filters were then washed several times with an ice-cold buffer using a Packard cell harvester. Bound radioactivity was measured with a scintillation counter (Topcount, Packard) using a liquid scintillation cocktail (Microscint 0, Packard). The effect of the individual

compounds on the specific radioligand binding to the selected receptors is shown in table 5. The values in table 5 are expresses as a per cent inhibition of specific radioligand binding in the presence of the test compound.

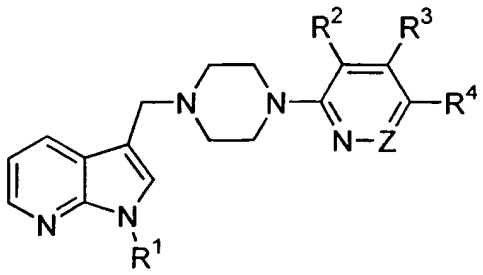
Table 5

Receptor	% Inhibition at 1 μM for Compound:			
	Compound A	Compound B	Compound C	Compound D
α2A	81	36	< 10	22
β1	< 10	< 10	< 10	ND
β2	< 10	< 10	< 10	ND
D1	34	37	< 10	< 10
D3	< 10	< 10	23	< 10
D5	29	27	10	< 10
M1	19	24	21	< 10
M2	20	17	< 10	< 10
M3	< 10	10	11	ND
5-HT1A	19	22	< 10	29
5-HT1B	28	14	< 10	ND
5-HT2A	73	86	23	< 10
5-HT2C	32	45	< 10	< 10
5-HT3	< 10	14	< 10	ND

ND = not determined

WE CLAIM:

1. A compound of Formula (I):



(I)

wherein Z is selected from N and C(R^5); R^1 is selected from H and an acid labile protecting group; R^2, R^3, R^4 and R^5 are independently selected from H, hydroxy, loweralkyl, loweralkyl optionally substituted with one or more groups selected from halo, hydroxy and loweralkoxy; loweralkyl-S-, halo, radioisotopic halo, loweralkoxy, trifluoromethylsulfonyl, cycloalkyl, aryl and tri(loweralkyl)tin; with the proviso that when Z is C(R^5) then at least one of R^2, R^3, R^4 and R^5 are selected from radioisotopic halo and tri(loweralkyl)tin; and salts, solvates or hydrates thereof.

2. A compound according to claim 1, wherein Z is N, R^1 is selected from H, alkoxycarbonyl and alkoxyalkyl, and R^2, R^3 and R^4 are independently selected from H, halo, radioisotopic halo, loweralkyl, loweralkoxy, hydroxy, phenyl, trifluoromethylsulfonyl, tributyltin and trimethyltin.

3. A compound according to claim 2, wherein R^1 is selected from H, *t*-butoxycarbonyl and methoxymethyl, and R^2, R^3 and R^4 are independently selected from H, I, Cl, Br, F, ^{123}I, ^{125}I, ^{131}I, ^{18}F, ^{76}Br, phenyl, tributyltin, trimethyltin and methoxy.

4. A compound according to claim 3, wherein R^1 is selected from H and *t*-butoxycarbonyl, and R^2, R^3 and R^4 are independently selected from H, I, Cl, ^{123}I, phenyl, methoxy and trimethyltin.

5. A compound according to any one of claims 1 to 4, wherein R^1 is H.

6. A compound according to any one of claims 1 to 5, wherein at least one of R^2, R^3 and R^4 is a radioisotopic halo.

7. A compound according to claim 6, wherein at least one of R^2, R^3 and R^4 is ^{123}I.

8. A compound according to claim 7, wherein R^4 is ^{123}I.

9. A compound according to claim 1, wherein Z is $C(R^5)$, R^1 is selected from H, alkoxycarbonyl and alkoxyalkyl, and R^2, R^3, R^4 and R^5 are independently selected from H, halo, radioisotopic halo, loweralkoxy, tributyltin and trimethyltin with the proviso that at least one of R^2, R^3, R^4 and R^5 are selected from radioisotopic halo, tributyltin and trimethyltin.

10. A compound according to claim 9, wherein R^1 is selected from H, *t*-butoxycarbonyl and methoxymethyl, and R^2, R^3, R^4 and R^5 are independently selected from H, ^{123}I, ^{125}I, ^{131}I, ^{18}F, methoxy, tributyltin, trimethyltin and methoxy with the proviso that at least one of R^2, R^3, R^4 and R^5 are selected from ^{123}I, ^{125}I, ^{131}I, ^{18}F, tributyltin and trimethyltin.

11. A compound according to claim 10, wherein R^1 is selected from H and *t*-butoxycarbonyl, and R^2, R^3, R^4 and R^5 are independently selected from H, ^{123}I, methoxy and trimethyltin with the proviso that at least one of R^2, R^3, R^4 and R^5 are selected from ^{123}I and trimethyltin.

12. A compound according to any one of claims 9 to 11, wherein R^1 is H.

13. A compound according to any one of claims 9 to 12, wherein at least one of R^2, R^3, R^4 and R^5 is a radioisotopic halo.

14. A compound according to claim 13, wherein at least one of R^2, R^3, R^4 and R^5 is ^{123}I.

15. A compound according to claim 14, wherein R^4 is ^{123}I.

16. A compound according to claim 1 selected from:

3-[4-(6-chloropyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(pyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(6-methoxy-5-trimethylstannylpyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(6-methoxy-5-iodopyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(6-methoxypyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo-[2,3-b]pyridine;
3-[4-(6-iodopyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
1-*t*-butoxycarbonyl-3-[4-(6-iodopyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
1-*t*-butoxycarbonyl-3-[4-(6-trimethylstannylpyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
^{123}I-3-[4-(6-iodopyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(6-methylpyridazin-3-yl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(6-iodo-5-methylpyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(6-hydroxypyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(6-trifluoromethanesulfonyloxypyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(6-phenylpyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(3,5-dichloropyridin-2-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
^{123}I-3-[4-(5-iodopyridin-2-yl)-piperazin-1-yl]methylpyrrolo[2,3-b]pyridine; and
1-t-butoxycarbonyl-3-[4-(5-trimethylstannylpyridin-2-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine.

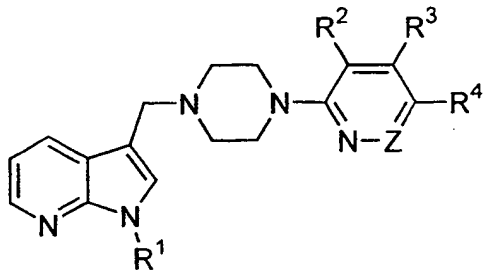
17. A compound according to claim 16 selected from:

3-[4-(6-chloropyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(pyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(6-methoxypyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo-[2,3-b]pyridine;
3-[4-(6-iodopyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
1-*t*-butoxycarbonyl-3-[4-(6-iodopyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
1-*t*-butoxycarbonyl-3-[4-(6-trimethylstannylpyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
^{123}I-3-[4-(6-iodopyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(6-methylpyridazin-3-yl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(6-phenylpyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
^{123}I-3-[4-(5-iodopyridin-2-yl)-piperazin-1-yl]methylpyrrolo[2,3-b]pyridine; and
1-t-butoxycarbonyl-3-[4-(5-trimethylstannylpyridin-2-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine.

18. A radiopharmaceutical composition, comprising a radiopharmaceutically acceptable carrier and a compound as defined in claim 6, 7, 8, 13, 14 or 15 in an amount effective to image a human brain.

19. A method of radioimaging a human brain, comprising the step of administering systemically to a patient a radiopharmaceutical composition as defined in claim 18, allowing the radiopharmaceutical to localize within the brain, and then taking an image of the brain of the patient so treated.

20. A pharmaceutical composition, comprising a pharmaceutically acceptable carrier and, in an amount effective to antagonize D4 receptor stimulation, a compound of the Formula:



wherein Z is N; R^1 is selected from H and an acid labile protecting group; and R^2, R^3 and R^4 are independently selected from H, hydroxy, loweralkyl, loweralkyl optionally substituted with one or more groups selected from halo, hydroxy and loweralkoxy; loweralkyl-S-, halo, loweralkoxy, cycloalkyl and aryl; and salts, solvates or hydrates thereof.

21. A pharmaceutical composition according to claim 20, wherein R^1 is selected from H, alkoxycarbonyl and alkoxyalkyl, and R^2, R^3 and R^4 are independently selected from H, halo, loweralkyl, loweralkoxy, hydroxy, and phenyl.

22. A pharmaceutical composition according to claim 21, wherein R^1 is selected from H, *t*-butoxycarbonyl and methoxymethyl, and R^2, R^3 and R^4 are independently selected from H, I, Cl, Br, F, phenyl and methoxy.

23. A pharmaceutical composition according to claim 22, wherein R^1 is selected from H and *t*-butoxycarbonyl, and R^2, R^3 and R^4 are independently selected from H, I, Cl, phenyl and methoxy.

24. A pharmaceutical composition according to any one of claims 20 to 23 , wherein R^1 is H.

25. A pharmaceutical composition according to claim 20 wherein said compound is selected from:

3-[4-(6-chloropyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(pyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(6-methoxy-5-trimethylstannylpyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(6-methoxy-5-iodopyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(6-methoxypyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo-[2,3-b]pyridine;
3-[4-(6-iodopyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
1-*t*-butoxycarbonyl-3-[4-(6-iodopyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(6-methylpyridazin-3-yl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(6-iodo-5-methylpyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(6-hydroxypyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(6-phenylpyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine; and
3-[4-(3,5-dichloropyridin-2-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine.

26. A pharmaceutical composition according to claim 25 wherein said compound is selected from:

3-[4-(6-chloropyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(pyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(6-methoxypyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo-[2,3-b]pyridine;
3-[4-(6-iodopyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
1-*t*-butoxycarbonyl-3-[4-(6-iodopyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine;
3-[4-(6-methylpyridazin-3-yl)piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine; and

3-[4-(6-phenylpyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-b]pyridine.

27. A method for treating a patient having a medical condition for which a D4 receptor antagonist is indicated, comprising the step of administering to the patient a pharmaceutical composition as defined in any one of claims 20 to 26.

28. A method for treating a patient according to claim 27, wherein the medical condition is schizophrenia.

29. A method for treating a patient according to claim 28, wherein the medical condition is anxiety.

INTERNATIONAL SEARCH REPORT

Inter ›nal Application No
PCT/CA 98/00615

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D471/04 A61K31/44 A61K31/555 A61K51/04 C07F7/22
//(C07D471/04,221:00,209:00)

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K C07F

Documentation searched other than minimumdocumentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 20497 A (MERK SHARP & DOHME) 15 September 1994 see page 2, line 18 - line 27; claim 1 & US 5 622 950 A (BAKER ET AL.) 22 April 1997 cited in the application & US 5 432 177 A (BAKER ET AL.) 11 July 1995 cited in the application --- -/--	1,20,28

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publicationdate of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of theinternational search	Date of mailing of the international search report
19 October 1998	27/10/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Alfaro Faus, I

INTERNATIONAL SEARCH REPORT

Inter ɔnal Application No
PCT/CA 98/00615

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	S. PATEL ET AL.: "Identification and pharmacological characterization of '125 I!L750,667, a novel radioligand for the dopamine D4 receptor" MOLECULAR PARMACOLOGY, vol. 50, no. 6, 1996, pages 1658-1664, XP002037689 New York see whole document ---	1,18
P,A	WO 97 46558 A (RESOLUTION PHARMACEUTICALS) 11 December 1997 see claims 1,18	1,18
P,A	& US 5 725 838 A (POLLAK ET AL) 10 March 1998 cited in the application -----	

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 98/ 00615

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 19, 27-29
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 19, 27-29 are directed to a diagnostic method or a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

...ormation on patent family members

Interr ...nal Application No
PCT/CA 98/00615

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9420497 A	15-09-1994	AU	674373 B	19-12-1996
		AU	5647094 A	08-09-1994
		BG	99885 A	29-02-1996
		BR	9406128 A	27-02-1996
		CA	2116213 A	02-09-1994
		CN	1118598 A	13-03-1996
		CZ	9502241 A	13-03-1996
		EP	0623618 A	09-11-1994
		FI	954088 A	31-08-1995
		HU	71799 A	28-02-1996
		JP	2710751 B	10-02-1998
		JP	6279442 A	04-10-1994
		NO	953406 A	31-10-1995
		NZ	261593 A	25-09-1996
		PL	310443 A	11-12-1995
		SI	9400091 A	31-12-1994
		SK	106395 A	06-12-1995
		US	5432177 A	11-07-1995
		US	5622950 A	22-04-1997
		ZA	9401368 A	28-10-1994
WO 9746558 A	11-12-1997	US	5725838 A	10-03-1998
		AU	2759897 A	05-01-1998